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ORAL ANTICOAGULANT DRUGS

All of the newer oral anticoagulant preparations are claimed to be superior to the old standby, bishydroxycoumarin U.S.P. (Dicumarol) in such characteristics as rapidity of onset, ease of maintenance, or rapidity of dissipation of effect. What about these claims?

Of the experts consulted in the preparation of this report, some still prefer Dicumarol; some favor warfarin (Coumadin-Endo; Athrombin--Purdue-Frederick). Phenprocoumon (Liquamar-Organon) and acenocoumarin (Sintrom-Geigy) also have their adherents. Some experts, including many in Britain, prefer the indandione anticoagulants. Because of greater variability of response, none of those consulted favored ethyl biscoumacetate (Tromexan-Geigy). Adding up the evidence and the opinions, the editors of The Medical Letter agree with those experts who find no sound basis for singling out any one of the drugs for therapeutic superiority. (Coumadin has the advantage of being the only oral anticoagulant that is also available in stable parenteral form.) On one point there is wide agreement: if the doctor is thoroughly familiar with any one of the drugs and is able to achieve good control with it, he should not change to another drug.

ONSET OF EFFECT - Rapid onset of effect is a desirable attribute in an oral anticoagulant, but none of the oral drugs act with sufficient rapidity to eliminate the initial use of heparin for prompt anticoagulation. One of the disadvantages of Dicumarol with conventional doses (300 mg. the first day and 200 mg. the second day) has been the long induction period. With a larger first-day dose (600 mg.), more rapid induction of peak levels can safely be achieved (T. Rodman, et al., Am. J. Med., 27:415, 1959). (These authors studied Dicumarol, diphenadione (Dipaxin-Upjohn), warfarin, and phenindione (Hedulin-Walter; Danilone-Schieffelin; Indon--Parke-Davis), and they conclude that "...none of the four drugs... appears to have enough advantages over the others to be recommended as the... agent of choice.")

The importance of quick dissipation of effect, an advantage claimed for some of the newer agents, is diminished by the ability of vitamin K_1 to restore prothrombin activity promptly should the need arise. As a matter of fact, slow dissipation may be a virtue in some circumstances. The prime need with any preparation is for predictable effect on prothrombin time, at least in the same patient, and for uniform effect from day to day. In this respect no one drug appears to be

consistently superior. The variability of response with any drug may be in some way related to variations in the patient's capacity to produce prothrombin, proconvertin and other coagulation factors. Occasionally a patient will show an unusual bleeding tendency, even when the prothrombin concentration is within the therapeutic range. In such patients, who may be difficult to manage with any drug, coagulation studies may indicate a deficiency of various blood factors. Periodic checks are necessary whenever there is suspicion that other deficiencies besides prothrombin are developing.

Whichever drug is used, frequent determinations of prothrombin time by a reliable laboratory are essential to determine the dosage required for adequate, smooth response, and to minimize the hazard of bleeding. A patient on anticoagulant therapy should carry with him at all times 5 mg. oral vitamin K_1 tablets (Mephyton-Merck). If slight bleeding occurs, 2.5 to 5 mg. will return the patient to the therapeutic range in about 12 hours. Then anticoagulant therapy is resumed as before. If more marked bleeding occurs, 20 mg. should be taken orally and when the patient reaches the physician's office, Mephyton emulsion can be injected. If life-threatening hemorrhage occurs, fresh whole blood transfusions are also used. The appearance of blood in the urine may give the first warning of anticoagulant bleeding; it often occurs without underlying renal disease.

CONTRAINDICATIONS AND SIDE EFFECTS - Anticoagulant drugs are contraindicated in (1) blood dyscrasias with bleeding tendencies; (2) hepatic or renal insufficiency; (3) severe hypertensive disease; (4) ulcerative lesions of the gastrointestinal tract; (5) subacute bacterial endocarditis; (6) threatened and incomplete abortions; (7) obstetric cases near term; (8) before surgery of any kind. The patient with uncontrolled congestive heart failure may be particularly difficult to control and sensitive to the toxic, bleeding effects of anticoagulant drugs. Dosage must be controlled with special care in patients who are receiving large doses of salicylic acid derivatives, phenothiazines, barbiturates, antibiotics, corticosteroids and ACTH. Long-term therapy should be employed only in patients who can fully cooperate and understand the risks of the disease and of the therapy. With

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DATA (ALL APPROXIMATE) ON ANTICOAGULANT DRUGS

	Onset of Peak Effect (Days)	Duration of Effect (Days)	First Day's Dose (mg.)	Maintenance Dose (mg.)	Cost of Maint. Dose
Dicumarol	2	4	600	100	5¢
Coumadin) Athrombin)	1.5	2 to 3	40-75	5-10	7-13¢
Tromexan	1 to 2	2	750 BID	150-450 BID	40¢-$1.10
Sintrom	1 to 2	3	20	2-10	9-45¢
Liquamar	1 to 2	4	30	1-6	4-20¢
Hedulin) Danilone) Indon)	1.5	2	200-250 BID	25-50 BID	3-6¢
Dipaxin	2	10 to 20	30-60	5	6¢

the coumarin derivatives, occasional side effects include vomiting, diarrhea, urticaria and maculo-papular eruptions. Indandione derivatives also have side effects, including sensitivity reactions (such as diarrhea, purpura and alopecia); a number of cases of agranulocytosis have also been reported. Except with patients who are sensitive to coumarin anticoagulants, it is doubtful that the indandiones have advantages over the coumarins which offset the possibility of serious side effects.

PENICILLIN

Despite the introduction of many new antibiotics, penicillin is still the most effective antibiotic against many organisms. But the frequency of anaphylactic, eczematous and delayed hypersensitivity reactions, especially from parenteral preparations, places a serious responsibility on the physician who uses it. Penicillin should never be used to treat self-limited or mild infections, or for routine pre- or post-operative prophylaxis. For the person not allergic to penicillin, it remains the antibiotic of choice for the prevention of rheumatic fever and subacute bacterial endocarditis, and for the treatment of severe infections by pneumococci, Group A hemolytic streptococci, penicillin-sensitive staphylococci, gonococci and Treponema organisms. In the penicillin-sensitive patient with these infections, the use of another antibiotic, such as erythromycin propionate, is mandatory.

Penicillin should never be administered without a careful check of the patient's history. A previous penicillin reaction of any kind, or a history of bronchial asthma, hay fever, or atopic eczema is an absolute contraindication to its use except in those rare instances in which an infection is life-threatening (as in bacterial endocarditis) and there is reason to believe that good results can be obtained only with penicillin. The presence of an active tinea infection of feet, groin or trunk is also a contraindication to the use of the drug, since a higher incidence of exfoliative reactions must be anticipated in such patients.

HYPERSENSITIVITY TEST - When the use of penicillin appears to be necessary despite such contraindications, a preliminary scratch test should be performed. The scratch test is more reliable and safer than intracutaneous or eye tests. A scratch 1/8" long is made through the epidermis of the inside of the forearm. One drop of a penicillin solution (diluted to contain 30,000 units per cc.) is placed on the scratch. A control scratch should also be made and one drop of saline solution placed on it. The test is read in 20 minutes. A wheal and erythema indicate a positive test. If there is a constitutional reaction, the penicillin should be wiped off, a tourniquet applied and epinephrine injected. If the scratch test is positive, other antibiotics must be employed. Even with a negative scratch test, however, anaphylactic or hypersensitivity reactions may occur.

If the scratch test is negative, the next step is not the administration of therapeutic doses, but the subcutaneous injection in the upper, outer arm, at intervals of about 2 to 4 hours, of graded small trial doses, starting with 500 units and successively doubling the dose. A tourniquet (for use around the arm) and epinephrine should be close at hand. When 300,000 units are reached, treatment may be carried on as usual.

Even in the absence of a history of allergy of any kind or of previous exposure to penicillin, the possibility of anaphylaxis should be kept in mind and the physician should be prepared to deal with the reaction before administration of the antibiotic. The simultaneous administration of parenteral antihistamine solutions with penicillin cannot be depended upon to prevent or control anaphylactic reactions; at best, parenteral antihistamines may inhibit some of the minor immediate reactions or early urticaria, but such masking may have the disadvantage of removing a valuable warning signal of marked sensitivity.

For immediate penicillin reactions, 0.4 cc. of epinephrine 1:1000 solution should be given intramuscularly or preferably intravenously. In hospital patients additional epinephrine may be given as a continuous infusion of 3 cc. per 500 cc. of 5% dextrose solution for adults. Delayed penicillin reactions can be treated with antihistamines by mouth, and with corticosteroids or ACTH. Penicillinase (Neutrapen-Schenlabs) has been successfully used in treating delayed penicillin reactions, but it should be remembered that penicillinase is itself an antigen capable of causing anaphylactic reactions (The Medical Letter, 3/6/59). Contrary to a widely held belief, procaine (in procaine-penicillin) is not a significant sensitizer.

VACCINES FOR RESPIRATORY VIRUS INFECTIONS

COLD VACCINES - The arrival of the season for upper respiratory infections has stimulated inquiries about cold vaccines. Regrettably, the answer is still negative: although several viruses which are believed to be responsible for the common cold have been isolated, no vaccine or any other medication is available that will prevent or abort a cold. Furthermore, it has not been shown that there is any merit whatsoever in the use of either oral or parenteral cold vaccines containing a variety of killed bacteria and intended to prevent colds or control secondary infections. The evidence for any treatment of the common cold must be examined in the light of the fact that, in many patients, the symptoms are responsive to placebo therapy.

ADENOVIRUS VACCINES - Effective vaccines are available against upper respiratory (and conjunctival) infections caused by some strains of adenoviruses. Epidemic adenovirus infections have been a problem at military installations, but such infection is too infrequent in the civilian population to warrant the use of the preventive vaccines except under special circumstances. There is no justification for the use of adenovirus vaccines as prophylaxis against the common cold.

INFLUENZA VACCINES - Although there is no indication at present of the emergence of pandemic influenza, some physicians consider it desirable to immunize patients having chronic cardiac or pulmonary disorders against influenza viruses A, A-1 (Asian) and B, one or more of which may cause endemic influenza in the coming months. A polyvalent A, A-1 and B virus vaccine is available (Parke-Davis, Lederle, Merck, Lilly and Pitman-Moore) and will provide about 60 per cent protection for several months against these strains. It will not protect against virus C strains, which may become more prevalent in coming months. Subcutaneous injection of the vaccine is more effective than the intradermal method. The vaccine should not be used in persons sensitive to chicken or egg protein.

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